We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 9

Mannan as a Promising Bioactive Material for Drug Nanocarrier Systems

Songul Yasar Yildiz and Ebru Toksoy Oner

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/58413

1. Introduction

Polysaccharides are natural, non-toxic and biodegradable polymers that cover the surface of most cells and play important roles in various biological mechanisms such as immune response, adhesion, infection and signal transduction. Investigations on the alternative treatments applied by different cultures throughout the history revealed the fact that the utilized plants and fungi were rich in bioactive polysaccharides with proven immunomodulatory activity and health promoting effects in the treatment of inflammatory diseases and cancer. Hence considerable research has been directed on elucidating the biological activity mechanism of these polysaccharides by structure-function analysis [1].

Hemicelluloses are structural polysaccharides which are the second most abundant heteropolymers present in nature accounting for one third of total components available in the plants (Figure 1) [2]. Mannans and xylans are the two most important hemicelluloses and hence a lot of research is mainly focused on their value-added applications and hydrolysis [3]. Mannan is a biodegradable and bioactive polysaccharide that has been a focus of interest by various sectors due to its valuable properties. The film forming capacity and biodegradability of mannans make them an interesting alternative to the petroleum-based materials. Mannan-based films and coatings were shown to exhibit low oxygen and grease permeability and, in some cases, relatively high tensile strength [4]. There are also interesting reports on the successful use of mannan as a bioactive material in health related applications.

Mannans are linear polymers of 1,4-linked mannose residues and contain less than 5% of galactose [5]. In nature, mannan is present in four different forms, each having a β-1,4-linked backbone containing mannose (linear mannan) or a combination of glucose and mannose residues (glucomannan) and occasional side chains of α-1,6-linked galactose residues (galac-

tomannan / galactoglucomannan). The mannose and glucose residues in the backbone are sometimes acetylated at C-2 or C-3 (3,5).

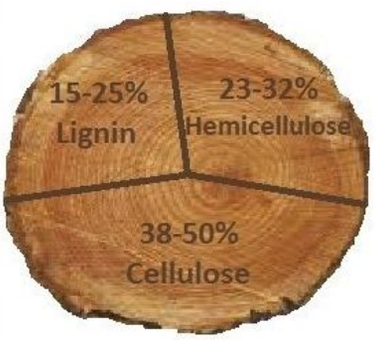

Figure 1. Polysaccharide composition of plants

In plants, mannans have a structural role by binding cellulose, but also they serve a storage function as a reserve carbohydrate in endosperm walls and vacuoles of seeds and vacuoles in vegetative tissues [5]. Recently, mannan has also been proposed as a signaling molecule in plant growth and development [6].

Mannan is a biodegradable and bioactive polysaccharide that has been a focus of interest by various sectors due to its valuable properties. The film forming capacity and biodegradability of mannans make them an interesting alternative to the petroleum-based materials. Mannan-based films and coatings were shown to exhibit low oxygen and grease permeability and, in some cases, relatively high tensile strength [4]. There are also interesting reports on the successful use of mannan as a bioactive material in health related applications. Mannan conjugated to vaccine preparations are already in the clinic [7,8]. Tang et al. [9] utilized a mannan-based system to target DNA vaccines to antigen presenting cells and demonstrated that it could induce far stronger immune responses in mice compared to naked DNA immunization. By further studies, they could explain the molecular basis of the observed immune enhancing attributes of mannan-based DNA vaccination [9]. Successful use of carboxylic mannan-coated iron oxide nanoparticles in targeting immune cells for *in vivo* lymph node-specific Magnetic Resonance Imaging was also reported recently [10]. Moreover, to target mannose receptor expressed on the surface of antigen-presenting cells, biocompatible self-assembled mannan nanogels were designed to provide a therapeutic or vaccine delivery platform [11,12]. In a recent review on oral drug delivery research in Europe, mannan based nanogels were considered as a new approach for the oral delivery of labile molecules [13].

In this chapter, after a brief description of mannan, its production by algae, fungi, bacteria and other eukaryotic microorganisms will be mentioned with special focus on microbial resources. Then, use of mannan as a bioactive material in nanocarrier systems for drug delivery applications will be covered in detail by giving examples from literature and industry. The final

http://dx.doi.org/10.5772/58413

section of the chapter will involve conclusions and future prospects on microbial mannan production and its potential uses in nanotechnology.

2. Structure of mannans

Mannan is one of the important member of the hemicellulose family and can be divided to four subfamilies: linear mannan, glucomannan, galactomannan, and galactoglucomanan [14]. Mannan is present in different forms, each having a β-1,4-linked backbone containing mannose (linear mannan) or a combination of glucose and mannose residues (glucomannan) and occasional side chains of α-1,6-linked galactose residues (galactomannan / galactoglucomannan) (Figure 2). In the backbone, mannose and glucose units can also be acetylated at C-2 or C-3 (3,5) .

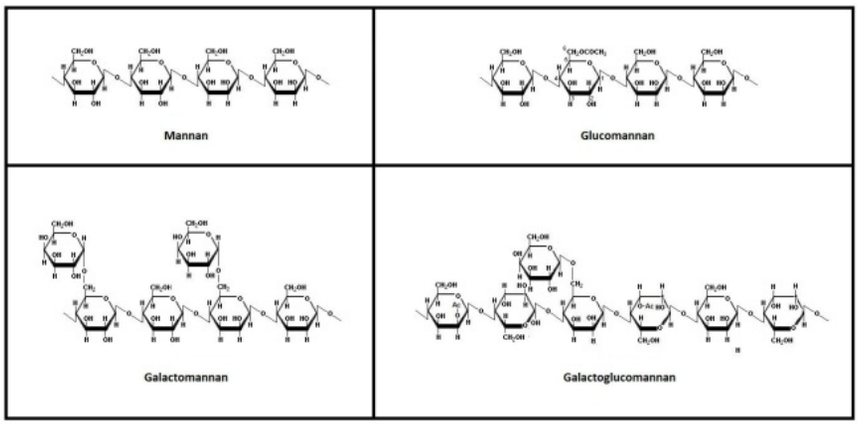

Figure 2. Four different forms of mannan

Glucomannan is mainly a straight-chain polymer, with a small amount of branching. The component sugars are β-(1,4)-linked D-mannose and D-glucose with a reported ratio of 1.6:1 [15], or 1.4:1 [16]. Softwoods and hardwoods consist of glucomannan with a glucose/mannose ratio of 1:3 and 1:1.5–2, respectively [17-20]. There is a significant similarity between conformation of glucomannan chains and those of cellulose A two-fold screw axis was observed because of the extended chains. Due to axial position of the hydroxyl group at C-2 of mannose, the interaction between C-6 and O-2 atoms of contiguous residues is prevented, and the chains are loosened, weakening the packing and organization [17]. Different structures were reported for glucomannans isolated from different sources. For example, (1 → 4)-linked structure, acetyl groups at C-2, C-3 positions and O-acetyl group at C-6 position were reported for glucomannan extracted from seeds of *Lupinus* [21]. Irregular distribution of acetyl groups was reported for pine glucomannan [22]. Studies on a nonionic glucomannan with a main chain of β-(1 → 4)-linked mannopyranosyl units to which D-glucopyranosyl units are linked by α-(1 → 6)

linkages, isolated from seeds of *Bryonia lacinosa* was also reported [23]. Galactomannans are polysaccharides consisting of 1,4-linked β-D-mannopyranose backbone with side chains of single 1,6-linked α-D-galactopyranose attached along the chain [24-26]. Galactose to mannose ratio show differences among different sources. More than 5% galactose residues can be considered as galactomannans [27].They are mainly found in the seeds of the family of *Leguminoseae* [28,29]. They are also present in the species of *Annonaceae*, *Convolvulaceae*, *Ebenaceae*, *Loganiaceae*, and *Palmae* [29]. Unusual backbone structure, containing (1 → 3)-linked residues together with a small proportion of (1 → 4)-linked β-D-mannopyranosyl residues with galactopyranosyl units attached at position 6, of galactomannan isolated from *Retama raetam* was reported in 2004 [30]. Presence of arabinosyl and glucosyl residues in the structure of galactomannans was observed in the studies of green and roasted coffee [31]. Several lichen species have been also reported as a source of galactomannan [32]. (1 → 6)-α-D-mannopyranosyl backbone with a different substitution pattern at O-2 and O-4 was observed in galactomannans isolated from lichens. The four major galactomannans of commercial importance in food and non-food industries are guar gum (GG, *Cyamopsis tetragonolobo*, M/G ratio: 2:1), tara gum (TG, *Caesalpinia spinosa*,M/G ratio: 3:1), locust bean gum (LBG, *Ceratonia siliqua*, M/G ratio: 3.5:1) and Fenugreek (*Trigonella foenum-graecum* L., M/G ratio: 1:1) [33].

Galactoglucomannan consists of a backbone of randomly distributed (1 → 4)-linked mannose and glucose units with (1 → 6)-linked galactose units attached to mannose units. The hydroxyl groups in locations C2 and C3 in mannose are partially substituted by acetyl groups [34,18]. Molar ratio of mannose, glucose and galactose was reported as 3:1:1 in the study of Puls and Schuseil [35]. Some of the mannosyl units are partially substituted by O-acetyl groups, equally distributed between C-2 and C-3 on the average one group per three to four hexose units [18, 36]. 5.9%-8.8% acetyl content was also observed [18].

The acetylated galactoglucomannan is mainly found in hemicellulose of softwoods. They can be either galactose rich or galactose poor with 10-15% and 5-8% of the dry woods respectively [36-38]. Acetylation at C-2 and C-3 positionsin the ratio of 2.2:1 was reported for galactoglucomannan backbone from native Norway spruce wood [36]. Formation of strong hydrogen bonds due to large content of D-galactose side-chains prevents the macromolecules from aligning themselves and hence galactoglucomannan is soluble in water [39].

3. Sources of mannans

Mannan is the predominant hemicellulosic polysaccharide in softwoods from gymnosperms, but is the minor hemicellulose in hardwood from angiosperms [35]. Unsubstituted beta-1,4-mannan, composed of a main chain of beta mannopyranose residues, is an important structural component of some marine algae [40] and terrestrial plants such as ivory nut [41] and coffee bean [42].

A variety of plants store energy in the form of mannans in their endosperm tissue, including members of the Palmae, Liliaceae, Iridaceae, and Leguminosae families [43,44]. Glucomannans also are used for energy storage in corms of plants within the genus Amorphophallus. In

http://dx.doi.org/10.5772/58413

addition to carbohydrate storage and structure, mannans serve a variety of other functions. In fern roots, mannans are deposited as constituents of cell wall appositions as a defense mechanism to limit microbial ingress [45]. Besides plants, algae are also a viable resource for mannan polysaccharides. In particular, the Dasycladalean alga Acetabularia acetabulum, also known as 'mannan weed', has long been known to contain mannan-rich walls [46]. Moreover, mannans are a common feature of fungal walls and a recent review points to the importance of cell surface mannans of pathogenic Candida species since they were found to participate in the adhesion to the epithelial cells, recognition by innate immune receptors and development of pathogenicity. Hence, clarification of the precise chemical structure of Candida mannan was reported as indispensable for understanding the mechanism of pathogenicity, and for development of new antifungal drugs and immunotherapeutic procedures [47]. Also, some yeast species stand out for their capability for excreting mannan to the fermentation medium. Yeast Rhodotorula acheniorum MC bioreactor cultures have been reported to produce 6.2 g/L mannan when grown for 96 hours in sucrose containing media [48]. Moreover, psychrophilic Antarctic yeast Sporobolomyces salmonicolor AL1 reached maximum glucomannan yield of 5.64 g/L in medium containing sucrose after a 5 days of fermentation [49]. Mannan synthesized by R. acheniorum MC, as well as the glucomannan, synthesized from strain *S. salmonicolor* AL_1 were both found to form stable emulsions making them suitable for various applications in pharmaceutical and cosmetic sectors [50]. On the other hand, studies also point to adverse toxic effects of fungal mannans when administered [51].

Although mannan production is established by numerious algal, fungi and other eukaryotic microorganisms, they are not normally products of bacteria [52]. There are only very few reported examples on extracellular mannan production by bacteria. Gram negative phytopathogenic bacterium *Pseudomonas syringae pv. ciccaronei* was reported to produce a highly branched phytotoxic mannopyranose polymer, which consisted of a backbone of α-(1,6)-linked mannopyranose units with 80% substituted at C-2 by mono-, di-and trisaccharide side chains [53]. Then, to understand the role of this mannan polymer in the activation of plant defence responses, various concentrations of the polymer was infiltrated in the abaxial side of tobacco leaves. Mannan polysaccharide was found to induce chlorotic and necrotic symptoms even at very low concentrations very effectively suggesting that it was identified by the plant cells as a signal of pathogen attack or environmental perturbation [54]. Two mannans at different chain lengths were reported to be produced by the marine bacterium *Edwardsiella tarda*, an opportunistic pathogen in human, and the polysaccharides were found to have good antioxidant and hydroxyl and DPPH radicals scavenging activities [55]. The lower molecular weight mannan was associated with higher antioxidant activity than the longer mannan and could be used as possible food supplement or ingredient in the pharmaceutical industry [55]. Recently, about 20-fold increase in mannan production has been reported in the pathogenic, constitutive biotin-producing *Pseudomonas mutabilis* bacteria [56]. The rheological properties of the highly branched mannan isolated from *P. mutabilis* T6 showed that its viscosity was over 30 times greater than that of the wild type *P. mutabilis* ATCC 31014.

Table 1. illustrates mannan producer organisms.

Source	Organism	Mannan type	Reference
Plant	*Ebenaceae* family	Galactomannan	[29]
Plant	*Arabidopsis thaliana*	Mannan	[57]
Plant	seeds of the family of *Leguminoseae*	Galactomannan	[28,29]
Plant	*Caesalpinia spinosa* Kuntze	Galactomannan	[33]
Plant	*Annonaceae* family	Galactomannan	[29]
Plant	*Amorphophallus konjac*	Glucomannan	[58]
Plant	*Ceratonia siliqua*	Galactomannan	[33]
Plant	*Convolvulaceae* family	Galactomannan	[29]
Plant	*Cyamopsis tetragonoloba*	Galactomannan	[33]
Plant	*Loganiaceae* family	Galactomannan	[29]
Plant	*Senna tora* seed	Galactomannan	[59]
Plant	*Trigonella foenum-graecum L.*	Galactomannan	[33]
Plant	*Palmae* family	Galactomannan	[29]
Plant	*Picea abies*	Galactoglucomannan	[60]
Plant	*Cercis siliquastrum*	Galactoglucomannan	[61]
Plant	*Nicotiana plumbaginifolia*	Galactoglucomannan	[62]
Yeast	*Hansenula holstii*	Phosphorylated mannan	[63]
Yeast	*Rhodotorula acheniorum*	Mannan	[48]
Yeast	*Sporobolomyces salmonicolor*	Glucomannan	[64]
Yeast	*Saccharomyces cerevisiae*	Mannan	[65]
Yeast	*Meyerozyma guilliermondii*	Mannan	[66]
Yeast	Brewers dried yeast	Mannan	[67]
Yeast	*Candida utilis*	Glucomannan	[68]
Algae	*Porphyra umbilicalis*	Mannan	[69]
Algae	*Acetabularia acetabulum*	Mannan	[46]
Algea	*Charophyceae*	Mannan	[70]
Fungus	*Dactylium dendroides*	Galactoglucomannan	[71]
Fungus	*Pseudocyphellaria clathrata*	Galactoglucomannan	[72]
Bacteria	*Pseudomonas mutabilis*	Mannan	[56]
Bacteria	*Pseudomonas syringae pv. ciccaronei*	Mannopyronose	[53]
Bacteria	*Edwardsiella tarda*	Mannan	[55]
Bacteria	*Pseudomonas aeruginosa*	Mannan	[73]
Bacteria	*Brevibacillus thermoruber*	Mannan	[74]

Table 1. Mannan producer organisms

http://dx.doi.org/10.5772/58413

4. Biosynthesis of mannans

Mannans are synthesized from activated nucleotide sugars such as GDP-mannose, GDP-glucose, and UDP-galactose [75]. Enzymes necessary for the nucleotide sugar conversion from sucrose to GDP-mannose and UDP-galactose have been reported in planta. However, the enzyme for the formation of GDP-glucose has not been identified [76]. Golgi-localized glycosyltransferases (GTs) utilize the activated nucleotide sugars and synthesize the polymer by facilitating the formation of the specific linkage between the monomers [77,78].

The cellulose synthase-like family A (CSLA) genes are considered the best candidates to encode enzymes that polymerize the backbones of β-linked noncellulosic polysaccharides [79,80]. Experimental evidence to support this hypothesis for the CslA family came first from Dhugga et al. [81]. In this research, the first β-mannan synthase (ManS), a member of the cellulose synthase-like family A (CSLA) from GT family 2, was identified in guar seeds (CtManS in Cyamopsis tetragonoloba, a AtCSLA9 ortholog) including the demonstration of its in vitro ManS activity [82]. One year later, three Arabidopsis CSLA genes were expressed in Drosophila Schneider 2 (S2) cells and demonstrated that the resulting CSLA proteins were capable of producing mannans when supplied with GDP-Man and glucomannans when provided with a mixture of GDP-Man and GDP-Glc [75]. CSLA genes appear to be present in all land plants, and ancestral genes with characteristics similar to CSLA sequences have been identified in a number of green algal genomes, in which they are thought to represent a homolog of the progenitor gene from which CSLA genes evolved [76]. In developing Trigonella foenum-graecum (Fenugreek) endosperm, a deep sequencing approach was used to identify genes involved in galactomannan biosynthesis [83]. This research reported a CSLA family protein involved in mannan backbone synthesis and a preference towards GDP-mannose as a donor substrate was observed from the activity assays with the heterologously expressed protein. Heterologously expressed CSLA proteins from a variety of species show mannan or glucomannan synthase activity in vitro [6,75,81,83]. Analysis of Arabidopsis CSLA mutants and over-expressing plants further confirmed that CSLA proteins function as glucomannan synthases *in vivo* [84]. Despite this progress in identifying and characterizing the enzymes responsible for galactoglucomannan biosynthesis, it is likely that other important enzymes are required, and many aspects of this process need to be better understood.

In tissues of *Arabidopsis*, that take role in tip-growth such as root hairs CSLD, (*At*CSLD2, 3 and 5) proteins were found to mediate mannan biosynthesis [85-92]. In Fenugreek, it was found that additional genes were involved in mannan biosynthesis, such as a golgi-localized mannan synthesis-related (*MSR*) gene that was observed in the fenugreek endosperm [83,93]. *Tf*MSR protein in Fenugreek and its homologs *AtMSR1* and *AtMSR2* in *Arabidopsis* were highly co-expressed with the ManS of the CSLA family. Glucomannan and ManS activity were significantly decreased in stems of *AtMSR* knock-out mutants [93]. While the biochemical activity of MSR proteins remains unknown, hypotheses include a role in primer synthesis to initiate mannan biosynthesis, the synthesis of oligosaccharides linked to CSLA or promoting folding, stability or activity of a mannan synthase complex [93].

Edwards et al. identified a mannan:galactosyltransferase (GalT) in *Trigonella foenum-graecum* [94], an enzyme that facilitates mannan *O*-acetylation. However, discovery of the involvement of a large plant-specific family of Trichome birefringence-like (TBL) proteins in *O*-acetylation of wall polymer as specific *O*-acetyltransferases suggested that this gene family encompassed a mannan *O*-acetyltransferase [95]. A highly expressed (among the 10 most abundant ESTs) homolog of *At*TBL25 in the *Amorphophallus konjac* deep sequencing database [96] revealed that this protein or the closely related *At*TBL26 could represent mannan *O*-acetyltransferase(s) in *Arabidopsis* [95].

5. Polysaccharide-based materials in drug delivery

Many properties of polysaccharides such as biocompatibility, solubility, potential for modification, and innate bioactivity provide great potential for their use in drug delivery systems (Figure 3).

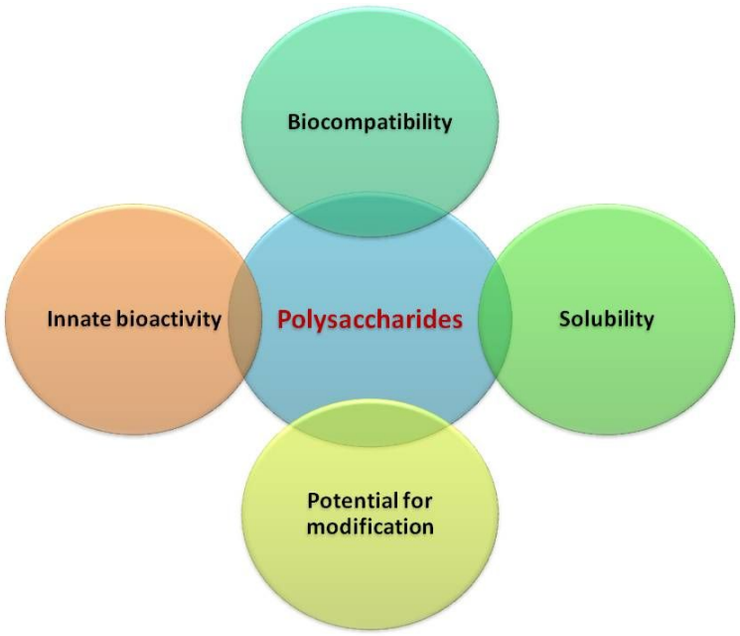

Figure 3. Properties of polysaccharides for potential use in drug delivery systems

Despite many synthetic polymers, polysaccharides have very low or no toxicity levels [97-100]. For example, dextrans are biopolymers composed of glucose with α-1,6 linkages, with possible branching from α-1,2, α-1,3, and α-1,4 linkages, that exhibit low toxicity and high biocompatibility, that makes them biocompatible hydrogels for controlled prolonged therapeutic release [101] and microspheres with no inflammatory response following subcutaneous injection into rats [102]. Since polysaccharides are naturally present in the body, most of them are degraded enzymatically. Through enzyme catalysis, polysaccharides can be broken down to their monomer or oligomer building blocks and recycled for use as storage,

http://dx.doi.org/10.5772/58413

structural support, or even cell signaling applications [103]. As a result, mechanism of release for therapeutics associated with polysaccharide-based carrier systems is provided by enzymatic degradation [104].

The functional groups of polysaccharides such as hydroxyl and amine groups yield high aqueous solubility. However, this solubility can often be adjusted via monomer modification. For example, *O*-acetylation of glucomannan can be used to modulate the formation of intermolecular hydrogen bonds with water, thereby altering aqueous solubility [105].

Due to the presence of various derivable groups on molecular chains, polysaccharides can be easily modified chemically and biochemically, resulting in many kinds of polysaccharide derivatives. These modifications can change the character of the polysaccharides. For instance, hydroxyl group oxidation enhances biodegradability, while sulfonation generates a heparin-like polysaccharide with increased blood compatibility [106]. Quaternization of the primary amines with various alkyl groups can be used to enhance solubility and alter bioactivity [107-109].

Many polysaccharides possess innate bioactivity, particularly mucoadhesive, antimicrobial, and anti-inflammatory properties. Positively charged polysaccharides are capable of binding to the negatively charged mucosal layers through charge interactions [110-112]. For neutral or negatively charged polysaccharides, hydrogen bonding provides an alternative mechanism for mucoadhesion [113]. Nanoparticle carriers made of bioadhesive polysaccharides could prolong the residence time and therefore increase the absorbance of loaded drugs [114]. Several polysaccharides are also antimicrobial in nature, such as chitosan [115]. Other polysaccharides are known to reduce inflammation. Anti-inflammatory activity is thought to be due to binding with immune-related acute phase and complement proteins [111,116] and polysaccharides are known to interact with a variety of proteins.

Nanocarriers are nanoparticle drug delivery systems that are used to deliver drugs or biomolecules. Nanocarriers are sub-micro particle structures smaller than 100 nm in at least one dimension and cover nanospheres, nanocapsules, nanomicelles, nanoliposomes, and nanodrugs, etc. Nanoparticle drug delivery systems have noticeable advantages. Due to the ultra-tiny volume of nanoparticle they can pass through the smallest capillary vessels and avoid rapid clearance by phagocytes, that lead to greatly prolonged duration in blood stream. Due to small dimensions, nanocarriers are able to cross the blood-brain-barrier (BBB) and operate on cellular level. They can easily penetrate cells and tissue gap to arrive at target organs such as spleen, spinal cord, liver, lung, and lymph. Because of the biodegradability, pH, ion and/or temperature sensibility of materials, they could show controlled release properties. They can improve the utility of drugs and reduce toxic side effects; etc. As drug delivery system, nanocarriers can entrap drugs or biomolecules into their interior structures and/or absorb drugs or biomolecules onto their exterior surfaces. Presently, nanoparticles have been widely used to deliver drugs, polypeptides, proteins, vaccines, nucleic acids, genes and so on.

In recent years, a large number of studies have been conducted on polysaccharides and their derivatives for their potential application as nanoparticle drug delivery systems [114,117-120] and among them, mannan is a very promising bioactive material for drug nanocarrier systems

since an amphiphilic form of mannan can spontaneously incorporate proteins and other agents, potentially providing a new nanostructure drug delivery system.

6. Medical potential of mannans as a drug nanocarrier systems

Glucomannans have a variety of applications, including food industry used as an emulsifier and thickener and medicine as a preventative of chronic disease and weight control agent [21]. Likewise, galactomannans also found many applications in food industrial as a thickener and food additive due to their rheological properties [121]. Moreover, galactomannans are widely used as versatile materials in industries such as textiles, paper, pharmaceutics, cosmetics, petroleum, drilling and explosives [93,122].

Galactomannans have also significant potential in medical applications such as innate immune system stimulation. On the other hand, the mannooligosaccharides (MOS) derived from these polysaccharides have also prebiotic activity for selective growth of Bifidobacterium spp., and Lactobacillus spp. [123]. They have also been described to present anticoagulation and fibrinolytic activity [124] and the MOS may prevent adherence of toxic bacteria to the intestinal wall, mediated by lectins, thus presenting anti-infectious potential [123,125,126].

In the research of Apostolopoulos *et al.* oxidized mannan conjugated to MUC1 fusion protein (M-FP) was used as a target for tumour immunotherapy and M-FP appeared to confer the survival/disease-free interval advantage in patients with early stage breast cancer [8].

In another study, the factors important to gene delivery and DNA vaccination that could contribute to the improved immunogenicity of oxidized mannan poly-L-lysine (OMPLL)–DNA and reduced mannan poly-L-lysine (RMPLL)–DNA immunization were investigated [9]. It was shown that OMPLL and RMPLL were able to complex with DNA to form particles that were taken up by charge dependent binding and endocytic pathways. High possibility of delivery of DNA was observed since the particles formed were able to protect DNA from DNase I digestion. More significantly, direct effect of OMPLL and RMPLL was observed on the antigen presentation of dentritic cells (DCs).

In 2010, Guo et al. reported that marine bacterium *Edwardsiella tarda* produced two extracellular polysaccharides ETW1 and ETW2, mannans with different molecular mass, that exhibited strong antioxidant activities [55]. To investigate the antioxidant activities of the two polysaccharides, antioxidant properties based on hydroxyl, DPPH radical scavenging and lipid peroxidation inhibition assays were carried out. The scavenging abilities of ETW1 and ETW2 on DPPH radicals, hydroxyl radicals and lipid peroxidation inhibition were concentration-dependent.

In 2011, Ferreira et al. prepared nanogel made of mannan [11]. The properties of the resulting nanogel were characterized and cytocompatibility was tested by using two cell lines, namely, mouse embryo fibroblasts 3T3 and mouse macrophage-like J774. The results of study revealed that the mannose receptor binds ligands at the cell surface and these receptor-ligand complexes were internalized via the endocytic pathway. Internalization of the nanogel caused cytotoxicity

since the non-phagocytic cell line was not affected and internalization was confirmed with J774. The high nanogel toxicity observed with the macrophage cell line indicated that the cell line J774 was not suitable for studies with mannan-C16 nanogel and primary cultures of macrophages that do not exhibit cytotoxicity should be used instead.

In 2012, the mannan nanogel cytocompatibility was tested in mouse embryo fibroblast cell line 3T3 and mouse bone marrow-derived macrophages (BMDM). [12]. The essential focus of the study was to assess nanomaterial cytocompatibility and to analyze the internalization by macrophages. The results of this study indicated that the mannan nanogel was biocompatible to mouse embryo fibroblast 3T3 cells and mouse BMDM. Essentially, no cytotoxic effect was observed with mannan nanogel up to about 0.4 mg/mL in *in vitro* experiments. Cell survival rate only dropped significantly at higher tested concentration after 48 h of incubation. Comet assay, under tested conditions, revealed no DNA damage in mouse embryo fibroblast 3T3 cells but possible DNA damage in mouse BMDM. Upon internalization by mouse BMDM mannan nanogel was localized in vesicles, as judged by the non-even distribution over the cytoplasm, and concentration of the fluorescence in internalized structures. Exit of nanogel from the mouse BMDM was observed when cells were incubated in fresh medium. Confocal colocalization image analysis denoted that the entrance and exit of nanogel and FM 4-64 might occur by the same processes – endocytosis and exocytosis – in BMDM.

Sato et al. [127] examined the adhesion inhibitory effect of mannan coating on acrylic denture surfaces against *Candida albicans* and *Candida glabrata*. The outermost layer of the *Candida* cell wall is covered with hydrophilic polysaccharides, such as mannan or galactomannan [128]. These mannans on the fungal surface function as adhesins, which are involved not only in the adhesion to the host cell [129,130] but also in the adsorption to plastic plates. On the other hand, when the plastic surfaces of culture dishes were coated with mannan, the adherence of *C. albicans* to the dishes was significantly inhibited [131,132]. The results of this study indicated that mannan inhibited the adhesion of *Candida* in a concentration-dependent manner, but mannose was not able to inhibit *Candida* adhesion even at a high concentration. The application of 0.1 mg/mL of mannan coating overnight showed inhibitory effects on the adhesion of the hyphal form of *C. albicans.* In the case of *C. glabrata*, the inhibitory effect was also observed to occur in a concentration-dependent manner, and the 10 mg/mL of mannan led to significantly higher anti-adhesive effects. This indicated that mannan effectively prevented the adhesion of two major *Candida* species to the denture surface, indicating the possibility of applying such a coating for clinical dentistry.

Superparamagnetic iron oxide nanoparticles (SPIONs) have been used as a contrast agent in magnetic resonance imaging (MRI) or as a carrier platform in the applications of drug [133-135] and gene delivery [137,138]. It was previously reported that mannan-coated SPION (mannan-SPION) could be specifically targeted to macrophages by the interaction with mannose receptors on antigen-presenting cells (APCs) [139]. Vu-Quang et al., [10] investigated the physicochemical properties, the *in vitro* and *in vivo* uptakes of carboxylic mannan-coated SPION (CM-SPION) using MRI and assessment of systemic toxicity. Results of the study showed that CM-SPION achieve longer circulation than mannan-SPION without compromising specificity. The intracellular accumulation of CM-SPION in macrophages was higher than

those of either PVA-SPIONs or Dex-SPIONs. The intracellular localization of CM-SPIONs was pre-dominantly observed in the cytoplasm of APCs. In the light of these results, authors claimed that CM-SPION could be regarded as a safe and potential contrast agent in LN-targeted MR imaging.

The effective conjugation of iron oxide nanoparticles with various biomolecules has been used for novel therapeutic-and drug delivery purposes [139-142]. Ultrasmall superparamagnetic iron oxide (USPIO) targets biomarkers of atherosclerotic plaques and improvements of USPIO make possible to obtain better plaque images at lower doses. Mannose units of mannan polysaccharides are recognized by mannose receptors on immune macrophages and they lack of significant toxicity. As a result, in the study of Tsuchiya [143], MRI-and histologic analyses were performed to compare the uptake by the rabbit atherosclerotic wall of four types of SPIO particles, i.e. SPIO, mannan-coated SPIO (M-SPIO), ultrasmall SPIO (USPIO), and mannan-coated USPIO (M-USPIO). Resuts of study reveal that mannan-coated iron particles had a greater affinity for active atherosclerotic plaques than non mannan-coated iron particles. Intracellular iron uptake was also higher in cells treated with M-USPIO than USPIO.

Glucomannans have diverse applications in biomedical and pharmaceutical areas due to the advantages of the polysaccharide such as weigt loss in obesity, decreased carbohydrate absorption in diabetes type 2, antitumor activity against sarcoma in cancer, decreased LDL levels in cholesterol, recognition of mannose receptors in targeting, antiseptic coating and sustained release profiles, increase of stability, improvement of the interaction between polmers, enhancement protein association of pharmaceutical forms of glucomannan. Glucomannan has been investigated as a pharmaceutical excipient in tablets, films, beads and hydrogels, due to its gelling, solubility and biodegradable properties [143-146].

Electrostatic interaction between the negative carboxylic groups of carboxymethylated-GM and the positive amino groups of chitosan was used for the preparation of nanoparticles made of carboxymethylated-GM and chitosan [147]. These nanoparticles were within size range of 50–1200 nm and exhibited a positive charge. Additionally, these nanoparticles elicited an ability to entrap and release bovine serum albumin (BSA) [147,148] The objection of use of GM in these nanoparticles was to increase their stability and their controlled release properties. Sande et al. reported that the introduction of GM into the nanoparticles lead to a facilitated interaction with the intestinal epithelium both *in vitro* and *in vivo* [149, 150]. The results of studies revealed that GM–chitosan nanoparticles offer attractive features as carriers for transmucosal drug delivery applications.

In the report of Zhang et al., use of konjac glucomannan (KGM) in oral colon targeting drug delivery system (OCDDS) was reviewed [151]. Based on the previous studies of KGM, it could be considered as a significant natural polysaccharide in OCDDS. It was known that KGM gel systems were able to maintain integrity and control the release of theophylline and diltiazem for 8 hours [152]. KGM hydrolysate was reported to have prebiotic potential for beneficial gut microbiota [153,154]. KGM is a water soluble polysaccharide because of hydrogen bonding in its structure [155,156]. The stronger the hydrogen bonding between their molecules, the harder for it to dissolve in water. Water solubility can be either advantageous or disadvangeous according to its application. Due to the high water adsorption rate, deficiency of free water in

gastrointestinal tract occurs and leads to diarrhea when KGM was used in the applications such as pharmaceutical excipients or drugs. On the other hand, when prepared as styptic sponge, which used to stop bleeding, the higher the water adsorption rate of it, the better the hemostasis effect may be. Modifications of KGM lead to alteration in the water adsorption of it. Moreover, KGM have gel-forming and film-forming properties [157].

In the previous studies, it was reported that KGM can be specifically degraded by colon β-mannanase [158], an enzyme generated by human colon bacteria [159]. On the other hand, based on the toxicity tests Ancui et al. reported KGM as a stable and safety material for medicinal purposes [160].

Invention of a novel hydrogel systems designed for colon-targeting drug delivery was reported in 2004 [158]. This hydrogel was composed of KGM, copolymerized with acrylic acid, and crosslinked by the aromatic azo agent bis(methacryloylamino)-azobenzene. Chen, Liu and Zhuo, copolymerized KGM and acrylic acid (AA) with N, N-methylene-bis-(acrylamide) (MBAAm) to form a novel hydrogel system [161]. Studies on swelling behaviors and degradation showed that the gel is pH-sensitive and could be degraded by Cellulase E0240 containing β-mannanase. Further researches demonstrated that the IPN hydrogel composed of KGM and poly(acrylic acid) (PAA) and cross-linked by N, N-methylene-bis-(acrylamide) (MBAAm) was still pH-sensitive and a potential carrier for colon-targeting drug delivery. Xu et al., prepared oxidized konjac glucomannan (OKG) for OCDDS which was pH-sensitive and could be used without the destruction of drugs in gastric acid [162]. Furthermore, Korkiatithaweechai et al., prepared controlled release of diclofenac sodium (DFNa) film from CTS (chitosan)-OKG [163]. This study suggested that the proportion of OKG in the formulation may affect the release profile and the formulation may be used for further study as a long term intestine controlled release drug model (at least 3 days), including as colon targeting drug carrier.

Guar gum derived from the seeds of *Cyamopsis tetragonolobus* is a naturally occuring galactomannan polysaccharide that consists of 80% galactomannan, 12% water, 5% protein, 2% acid insoluble ash, 0.7% ash and 0.7% fat. Guar gum has been reported as an inexpensive and flexible carrier for oral extended release drug delivery [164]. Guar gum can be used for colon delivery since it can be degraded by specific enzymes in this region of the gastrointestinal tract. GG provides protection to the drug in the environment of the stomach and small intestine, and drug delivery to the colon where it is degraded by the enzymes excreted by specific microorganisms. Guar gum shows high potential as a carrier for oral controlled release matrix systems. Furthermore, excipients to GG can be used to modulate drug release from these matrix systems [165].

Locust bean gum also known as Carob bean gum consists mainly of a neutral galactomannan polymer made up of 1,4-linked D-mannopyranosyl units and every fourth or fifth chain unit is substituted on C6 with a D-galactopyranosyl unit. Locust bean gum is a neutral polymer and its viscosity and solubility are therefore little affected by pH changes within the range of 3-11 [166]. Locust bean gum was used to produce matrix tablets with and without the cross-linker, glutaraldehyde [101]. A commercially available tablet system (TIMERx®) developed

by Penwest Pharmaceuticals Company consisting of locust bean gum and xanthan gum showed both *in vitro* and *in vivo* controlled release potential [167].

Guar gum hydrates and swells in cold water [168]. This gelling cause to retardation of the drug release from the tablets [169,170]. Guar gum is being used to deliver drug to the colon due to its drug release retarding property and susceptibility to microbial degradation in the large intestine [171,172]. Guar gum based matrix tablets of dexamethasone and other antinflammatory agents were prepared and used in colon targeting [173]. Whereas negligible drug release was observed in simulated gastric and intestinal fluids, significant increase in drug release was reported in simulated colonic fluid.

Colonic drug delivery system based on pectin (polygalactronic acid) and galactomannan coating was reported by Lee et al. [174] and Pai et al. [175]. These two polysaccharides, pectin and galactomannan, were used as coating material of a conventional tablet or capsule. The coating of pectin/galactomannan mixture was shown to be strong, elastic and insoluble in simulated gastric and intestinal fluids such that it would protect drug from being released in the upper GI tract. Researches revealed that in the colon, bacterial degradability was preserved. Moreover, extended film resistance to hydration, subsequent solubilization, film degradation rate by enzymes and drug release rate were found to depend on the varying ratio of pectin to galactomannan. Higher galactomannan percentage caused to decreased bacterial degradation in the colon and prolonged duration of negligible drug release in the upper GI tract. Compared with the combination of pectin and ethyl cellulose [176] or amylose and ethyl cellulose [177], combination of pectin and galactomannan was advantageous due to faster *in vivo* degradation of both pectin and galactomannan by microflora in the colon.

Matrix tablet of indomethacin with guar gum was prepared and the suitability of guar gum as a carrier in colonic drug delivery was investigated in another study [178]. The results indicated the specificity of these matrices for enzymes triggered the drug release in the colon. In another *in vivo* study, matrix tablets containing around 77% guar gum were loaded with technetium-99m-DTPA as tracer and scintigraphs were taken at regular intervals in six healthy human male volunteers [179]. These tablets were found to remain intact releasing only small amount of tracer in the stomach and the small intestine. However, bulk of the tracer was released in the ascending colon thereby suggesting that the enzyme triggered degradation by colonic bacteria.

Rubinstein and Gliko-Kabir investigated a biodegradable property of guar gum cross-linked with borax [180]. The time required for degradation of these crosslinked guar gum and borax showed that release of drug would be in proximal colon. The same group analysed phosphated cross-linked guar gum hydrogels for their potential as colon drug carriers *in vitro* and *in vivo* in 2000 [181]. *In vitro* studies revealed that these hydrogels loaded with hydrocortisone were able to resist the release of 80% of the drug for 6 h in phosphate buffer. *In vivo* studies in rat showed that degradation of modified guar gum by enzymes was concentration dependent. Thus, the phosphated crosslinked guar gum could be considered suitable for colon drug delivery.

http://dx.doi.org/10.5772/58413

Alginate is a non-toxic polysaccharide that have properties such as pH sensitivity. This pH sensitivity is favorable for intestinal delivery of protein drugs. However, drug leaching during hydrogel preparation and rapid dissolution of alginate at higher pH are major limitations since when it enters the intestine, these limitations cause to very low entrapment efficiency and burst release of entrapped protein drug. To overcome these limitations, George and Abraham used another natural polysaccharide, guar gum which is included in the alginate matrix along with a cross linking agent to ensure maximum encapsulation efficiency and controlled drug release [182].

In the study of Coviello et al. [101], two galactomannans, guar gum and Locust bean gum, have been investigated for their possible use as matrices for modified drug delivery. They were crosslinked with glutaraldehyde (Ga) and then used for the preparation of tablets. This preparations increased the rate of release of small guest molecules due to the fact that the chemical reaction with Ga introduced meshes with a size larger than those present in the simply entangled systems.

In the study of Voepel et al. [183], hydrogels based on acetylated galactoglucomannan (AcGGM) were synthesized and examined for their properties in drug-release systems using two model substances of different molecular weight, size, and polarity (caffeine and vitasyn blue). AcGGM was synthetically modified to yield a polysaccharide with either neutral or ionic pendant groups. These precursors were formulated to produce either a neutral, covalent hydrogel or a physically cross linked hydrogel. Neutral and ionic hydrogels based on HEMA-Im– modified AcGGM (M-AcGGM) and maleic anhydride modified M-AcGGM (CM-AcGGM) were studied in view of their chemical, physical and drug release properties. In the case of the neutral hydrogels, half of the total drug release (50 wt % release) was reported to occur between 13 and 35 min and 50 to 90 min for caffeine and vitasyn blue, respectively. The majority of the caffeine (80 wt %) was released between 40 and 120 min, on the other hand, the majority of vitasyn blue was released between 125 and 250 min. When maleic anhydride was added to the M-AcGGM, ionic poly(CM-AcGGMco-HEMA) hydrogels could be achieved. Slower release of caffeine was found in these hydrogels, especially at acidic conditions because of the pH responsitivity obtained through the introduced carboxylic functionalities.

Roos et al. synthesized hydrogels from *O*-acetyl-galactoglucomannan (AcGGM) with encapsulated bovine serum albumin (BSA), to investigate the influence of substitutions and the feasibility of BSA-release mediated by the addition of β-mannanase to hydrolyze the hydrogel [184]. Hydrogels were prepared from AcGGM substituted with various amounts of 2-hydroxyethylmethacrylate groups and loaded with BSA. The degree of substitution of HEMA and the presence of β-mannanase *An*Man5A were two parameters that influenced the release of BSA from the hydrogels in water. Increasing HEMA substitutions on the glucomannan backbone from 0.1 to 0.36 caused lesser spontaneous release of BSA. However, the addition of β-mannanase *An*Man5A increased the BSA release due to enzymatic hydrolysis of AcGGM. The hydrogel with DS_{HEMA} (degree of sustitution) 0.36 released almost all remaining BSA from the hydrogel within 8 h after addition. The results of the study provided significant insights into further developments of AcGGM-based hydrogels for the application of drug delivery

Bioadhesive poly(D,L-lactide-co-glycolide) (PLGA) nanoparticles were reported as promising drug delivery systems [185], and surface modification of nanocarriers was provided by application of mannan-based PE-grafted ligands (MAN-PEs) [186]. Kong et al. investigated MAN-PE-modified bioadhesive PLGA nanoparticles as active targeting gene delivery system using plasmid enhanced green fluorescent protein (*pEGFP*) as the model gene [187]. In the reported study, in order to achieve active targeting to the liver, surface of of PLGA nanoparticles was modified by the application of MAN-PEs. *In vitro* and *in vivo* behavior of mannan-modified DNA-loaded PLGA nanoparticles were compared with nonmodified DNA-loaded PLGA nanoparticles. Spherical shapes were observed for nonmodified DNA-NPs while the mannan-modified MAN-DNA-NPs had a dark coat on the white balls, that indicated the successful coating of mannan-PE. The mean particle size of NPs was around 100–200 nm, which was ideal for the nanoparticulate system. MAN-PEs-modified *pEGFP*-loaded bioadhesive PLGA-NPs could be targeted to the liver and successfully transfected the Kupffer cells (KCs).

In the study of Wu et al., mannan-PEG-PE (MN-PEG-PE) modified bioadhesive PLGA nanoparticles were obtained as a targeted gene delivery system [188]. Mannan was the target part that bind to the mannose receptor (MR) in the macrophage, and PEG-PE was the spacer linked into the surface of NPs. The results of this study confirmed that mannose-mediated targeting could successfully deliver genes into MR expressing cells. Improved transfection efficiency was observed in the case of mannose containing targeting ligands, such as in DNA loaded PLGA NPs. The results supported the active targeting ability of mannan containing PEG-PE modified bioadhesive PLGA nanoparticles, and the resulting vectors would be very useful in gene delivery both *in vitro* and *in vivo.*

In the study of Kaur, sustained and targeted release nanoparticles of didanosine were formulated using gelatin as polymer and mannan-coating to further enhance its macrophage uptake and its distribution in organs that act as major reservoirs of HIV [189]. Coating of nanoparticles with mannan further retarded the drug release (42.5 ± 1.7% over 24 h) and increased the cellular uptake of nanoparticles (N-C3-M) as was evident by higher staining intensity and complete lysis within 2 h of incubation. The better cellular uptake of mannan-coated nanoparticles might be due to the presence of mannosyl receptor predominantly on the macrophage cell surface, which was used by the cells for endocytosis and phagocytosis [190,191]. The results showed higher accumulation of didanosine in brain when administered through mannan-coated nanoparticles. Didanosine is a hydrophilic drug and its ability to cross the blood brain barrier was very low; however, mannan-coated nanoparticles provided enhanced delivery of didanosine to brain. Hence, mannan-coated gelatin nanoparticles resulted in a significantly higher concentration of didanosine in spleen, lymph nodes and brain.

7. Future prospects

Overview of literature clearly shows the high potential of mannan-based biomaterials in health related applications. In these studies though, the monomer composition and structure of mannan polysaccharide plays the key role for a successful design. It is well known that the

composition of polysaccharides is highly influenced by the environmental conditions and strictly depends on the availability of the activated sugar monomers. Currently, main sources for mannan are plants, algae and fungi where production may take months and greatly depends on geographical or seasonal conditions. On the other hand, microbial sources could be a feasible alternative for the sustainable and economical production of mannan at industrial scale. Microbial fermentation would not only enable the use of low-cost resources for the economical production, but also provide control over the chemical structure, monomer composition and physicochemical and rheological properties of the final product. There are only few reports on microbial mannan production and from these, thermophiles stand out with their high production rates due to their high metabolic activity. Moreover, such simple systems enable the effective application of systems-based approaches to obtain tailor-made polymers.

Finally, mannan is a very promising bioactive material for drug nanocarrier systems since its amphiphilic structure can incorporate diverse biomolecules, potentially providing novel nanostructure drug delivery systems. Hence, development of high mannan producer cell factories would overcome the problems associated with the sustainable production of this important biomaterial.

Author details

Songul Yasar Yildiz and Ebru Toksoy Oner*

*Address all correspondence to: ebru.toksoy@marmara.edu.tr

Industrial Biotechnology and Systems Biology Research Group, Department of Bioengineering, Marmara University, Istanbul, Turkey

References

[1] Ramberg JE., Nelson ED., Sinnott RA. Immunomodulatory dietary polysaccharides: a systematic review of the literature. Nutrition Journal 2010; 9(54).

[2] Harris PJ., Stone BA. Chemistry and molecular organization of plant cell walls. In: Himmel ME. (ed.) Biomass recalcitrance. Blackwell: Oxford; 2008. pp 60–93.

[3] Chauhan PS., Puri N., Sharma P., Gupta N. Mannanases: microbial sources, production, properties and potential biotechnological applications. Applied Microbiology and Biotechnology 2012;93(2) 1817–1830.

[4] Mikkonen KS., Tenkanen M. Sustainable food-packaging materials based on future biorefinery products: xylans and mannans. Trends in Food Science & Technology 2012;28(2) 90-102.

[5] Moreira LRS., Filho EXF. An overview of mannan structure and mannan degrading enzyme systems. Applied Microbiology and Biotechnology 2008;79(2) 165–178.

[6] Liepman AH., Nairn CJ., Willats WGT., Sørensen I., Roberts AW., Keegstra K. Functional genomic analysis supports conservation of function among cellulose synthase-like A gene family members and suggest diverse roles of mannans in plants. Plant Physiology 2007;143 1881–1893.

[7] Pashov A., Monzavi-Karbassi B., Kieber-Emmons T. Glycan-mediated immune responses to tumor cells. Human vaccines 2011; 7 156-165.

[8] Apostolopoulos V., Pietersz GA., Tsibanis A., Tsikkinis A., Drakaki H., Loveland BE., Piddlesden SJ., Plebanski M., Pouniotis DS., Alexis MN., McKenzie IF., Vassilaros S. Pilot phase III immunotherapy study in early-stage breast cancer patients using oxidized mannan-MUC1 [ISRCTN71711835]. Breast Cancer Research 2006; 8 R27.

[9] Tang CK., Sheng KC., Esparon SE., Proudfoot O., Apostolopoulos V., Pietersz GA. Molecular basis of improved immunogenicity in DNA vaccination mediated by a mannan based carrier. Biomaterials 2009;30 1389-400.

[10] Vu-Quang H., Muthiah M., Kim YK., Cho CS., Namgung R., Kim WJ., Rhee JH., Kang SH., Jun SY., Choi YJ., Jeong YY., Park IK. Carboxylic mannan-coated iron oxide nanoparticles targeted to immune cells for lymph node-specific MRI *in vivo.* Carbohydrate Polymers 2012; 88 780-788.

[11] Ferreira SA., Pereira P., Sampaio P., Coutinho PJG., Gama FM. Supramolecular assembled nanogel made of mannan. Journal of Colloid Interface Science 2011;361 97.

[12] Ferreira SA., Carvalho V., Costa C., Teixeira JP., Vilanova M., Gama FM. Self-Assembled Mannan Nanogel: Cytocompatibility and Cell Localization. Journal of Biomedical Nanotechnology 2012; 8 1-9.

[13] Mrsny RJ. Oral drug delivery research in Europe. Journal of Controlled Release 2012;161 247-253.

[14] Petkowicz CLO., Reicher F., Chanzy H., Taravel FR., Vuong R. Linear mannan in the endosperm of *Schizolobium amazonicum*. Carbohydrate Polymers 2001;44 107–112.

[15] Kato K.., Matsuda K. Studies on the chemical structure of konjac mannan Part I. Isolation and characterization of oligosaccharides from the partial acid hydrolyzate of the mannan. Agricultural and Biological Chemistry 1969; 33 1446–1453.

[16] Bewley JD., Reid JSG. Mannans and glucomannans. In: Dey PM:, Dixon RA. (ed.) Biochemistry of storage carbohydrates in green plants. New York: Academic Press; 1985. p 289 –304.

[17] Northcote DH. Chemistry of the plant cell wall. Annual Review of Plant Physiol ogy 1972;23 113–132.

[18] Popa VI., Spiridon J. Hemicelluloses: structure and properties. In: Dumitriu S. (ed.) Polysaccharides: structural diversity and functional versatility. New York: Marcel Dekker; 1998. p 297–311.

[19] Timell TE. Recent progress in the chemistry of wood hemicelluloses. Wood Science Technology 1967;1 45–70.

[20] Hongshu Z., Jinggan Y., Yan Z. The glucomannan from ramie. Carbohydr Polymers 2002;47 83–86.

[21] Ishurd O., Kermagi A., Elghazoun M., Kennedy JF. Structural of a glucomannan from *Lupinus varius* seed. Carbohydr Polymers 2006;65 410–413.

[22] Kenne L, Rossel KG., Svensson S. Studies on the distribution of the O-acetyl groups in pine glucomannan. Carbohydrate Research 1975; 44 69–76.

[23] Singh V., Malviya T. A non-ionic glucomannan from the seeds of an indigenous medicinal plant: Bryonia lacinosa. Carbohydrate Polym ers 2006;64 481–483.

[24] McCleary BV., Matheson NK. Polysaccharides having a β-D-xylan backbone. Advance Carbohydrate Chemistry and Biochemistry 1986;44 158–164.

[25] Shobha MS., Kumar ABV., Tharanathan RN., Koka R., Gaonkar AK. Modification of guar galactomannan with the aid of *Aspergillus niger* pectinase. Carbohydrate Polymers 2005;62 267–273.

[26] Parvathy KS., Susheelamma NS., Tharanathan RN., Gaonkar AK. A simple non-aqueous method for carboxmethylation of galactomannans. Carbohydrate Polym ers 2005; 62 137–141.

[27] Aspinall GO. Structural chemistry of the hemicelluloses. In: Wolfrom ML., Tipson RS. (ed.) Advances in carbohydrate chemistry. Newyork and London : Academic Press; 1959 p429-468.

[28] Dea ICM., Morrison A. Chemistry and interactions of seed galactomannans. Advance Carbohydrate Chemistry and Biochemistry 1975;31 241–312.

[29] Dey PM. Biochemistry of plant galactomannans. Advance Carbohydrate Chemistry and Biochemistry 1978;35 341–376.

[30] Ishurd O., Kermagi A., Zgheel F., Flefla M., Elmabruk M., Yalin W., Kennedy JF., Yuanjiang P. Structural aspects of watersoluble galactomannan from the seeds of *Retama raetam*. Carbohydrate Polymers 2004;58 41–44.

[31] Nunes FM., Domingues MR., Comibra MA. Arabinosyl and glucosyl residues as structural features of acetylated galactomannans from green and roasted coffee infusions. Carbohydrate Research 2005;340 1689–1698.

[32] Omarsdottir S., Petersen BO., Barsett H., Paulsen BS., Duus JØ., Olafsdottir ES. Structural characterization of a highly branched galactomannan from the lichen *Peltigera*

canina by methylation analysis and NMR-spectroscopy. Carbohydrate Polym ers 2006;63 54–60.

[33] Prajapati VD., Jani GK., Moradiya NG., Randeria NP., Nagar BJ., Naikwadi NN., Variya BC. Galactomannan: a versatile biodegradable seed polysaccharide. International Journal of Biological Macromolecules 2013;60 83-92.

[34] Aspinall GO., Begbie R., McKay JE. The hemicelluloses of European larch (*Larix decidua*). Part II. Journal of Chemical Society 1962;214:219

[35] Puls J., Schuseil J. Chemistry of hemicellulose: relationship between hemicellulose structure and enzyme required for hydrolysis. In: Coughlan MP., Hazlewood GP. (ed.) Hemicellulose and hemicellulases. London:Portland; 1993. p 1–27.

[36] Willför S., Sjöholm R., Laine C., Roslund M., Hemming J., Holmbom B. Characterisation of water-soluble galactoglucomannan from Norway spruce wood and thermomechanical pulp. Carbohydrate Polymers 2003;52 175–187.

[37] Lundqvist J., Teleman A., Junel L., Zacchi G., Dahlman O., Tjerneld F., Stålbrand H. Isolation and characterization of galactoglucomannan from spruce (*Picea abies*). Carbohydrate Polymers 2002; 48 29–39.

[38] Lundqvist J., Jacobs A., Palm M., Zacchi G., Dahlman O., Stålbrand H. Characterization of galactoglucomannan extracted from spruce (*Picea abies*) by heat-fractionation at different conditions. Carbohydrate Polymers 2003;51 203–211.

[39] Timell TE. Wood Hemicelluloses: part II. Carbohydrate Chemistry 1965;20 409–483.

[40] Yamasaki T., Miyazaki Y., Kamei Y. Isolation of bacteria that decompose major polysaccharides in the cell wall of the marine red alga *Porphyra yezoensis* and their application for protoplast production. Canadian Journal Microbiology 1998;44 789–794.

[41] Chanzy H., Dube M., Marchessault RH., Revol JF. Single crystals and oriented crystallization of ivory nut mannan. Biopolymers 1979;18 887-898.

[42] Nunes FM., Reis A., Domingues MR., Coimbra MA. Characterization of galactomannan derivatives in roasted coffee beverages. Journal of Agricultural and Food Chemistry 2006;54 3428–3439.

[43] Meier H. and Reid JSG. Reserve polysaccharides other than starch in higher plants. In: Loewus FA. and Tanner W. (ed.) Plant Carbohydrates I, Intracellular Carbohydrates Verlag: Berlin, Heidelberg and New York: Springer; 1982. pp 418-471.

[44] Buckeridge MS. Seed cell wall storage polysaccharides: models to understand cell wall biosynthesis and degradation. Plant Physiology 2010;154 1017–1023.

[45] Leroux O., Leroux F., Bagniewska-Zadworna A., Knox JP., Claeys M., Bals S., Viane RL. Ultrastructure and composition of cell wall appositions in the roots of *Asplenium* (Polypodiales). *Micron* 2011; 42 863–870.

[46] Dunne EK., Shoue DA., Huang X., Kline RE., Mackay AL., Carpita NC., Taylor IEP., Mandoli DF. Spectroscopic and biochemical analysis of regions of the cell wall of the unicellular 'mannan weed' *Acetabularia acetabulum*. Plant Cell Physiology 2007;48 122–33.

[47] Shibata N., Kobayashi H., Suzuki S. Immunochemistry of pathogenic yeast, *Candida* species, focusing on mannan. Proceeding of Japan Academy Ser B 2012;88(6) 250-265.

[48] Pavlova, K., Panchev, I., Hristozova, T. Physico-chemical characterization of exo-mannan from Rhodotorula acheniorum MC. World Journal of Microbiology & Biotechnology 2005);21 279–283.

[49] Poli A., Anzelmo G., Tommonaro G., Pavlova K., Casaburi A., Nicolaus B. Production and chemical characterization of an exopolysaccharide synthesized by psychrophilic yeast strain *Sporobolomyces salmonicolor* AL1 isolated from Livingston Island, Antarctica. Folia Microbiologica 2011;55(6) 576.

[50] Kuncheva M., Pavlova K., Panchev I., Dobreva S. Emulsifying power of mannan and glucomannan produced by yeasts. International Journal of Cosmetic Science 2007; 29 377–384.

[51] Ataoglu H., Dogan MD., Mustafa F., Akarsu ES. *Candida albicans* and *Saccharomyces cerevisiae* cell wall mannans produce fever in rats: role of nitric oxide and cytokines. Life Sciences 2000;67(18) 2247–2256.

[52] Sutherland IW. Bacterial Exopolysaccharides. In: Kamerling JP. (ed.) Comprehensive glycoscience. Amsterdam: Elsevier; 2007 pp 521-557.

[53] Corsaro MM., Evidente A., Lanzertta R., Lavermicocca P., Molinaro A. Structural determination of the phytotoxic mannan exopolysaccharide from *Pseudomonas syringae* pv. *ciccaronei*.Carbohydrate Research 2001;330 271-277.

[54] Pinto MC., Lavermicocca P., Evidente A., Corsaro MM., Lazzaroni S., De Gara L. Exopolysaccharides produced by plant pathogenic bacteria affect ascorbate metabolism in *Nicotiana tabacum*. Plant Cell Physiology 2003;44(8) 803–810.

[55] Guo S., Mao W., Han Y., Zhang X., Yang C., Chen Y., Chen Y., Xu J., Li H., Qi X., Xu J. Structural characteristics and antioxidant activities of the extracellular polysaccharides produced by marine bacterium *Edwardsiella tarda.* Bioresource Technology 2010; 101(12) 4729-4732.

[56] Kuzma M., Clarck B., Edwards J., Tylingo R., Samaszko J., Madaj J. Structure and properties of the exopolysaccharides produced by *Pseudomonas mutabilis* T6 and *P. mutabilis* ATCC 31014. Carbohydrate Research 2012; 348 84-90.

[57] Handford MG, Baldwin TC, Goubet F, Prime TA, Miles J, Yu X, et al. Localisation and characterisation of cell wall mannan polysaccharides in Arabidopsis thaliana. Planta. 2003;218(1):27-36.

[58] Fang W., Wu P. Variations of Konjac glucomannan KGM from Amorphophallus konjac and its refined powder in China. Food Hydrocolloids 2004;18(1) 167-170.

[59] Pawar HA., Lalitha KG. Isolation, purification and characterization of galactomannans as an excipient from *Senna tora* seeds. International Journal of Biological Macromolecules 2014; 65 167-175.

[60] Capek P., Kubackova M., Alföldi J., Bilisics L., Liskova D., Kakoniova D. Galactoglucomannan from the secondary cell wall of *Picea abies* L. Karst. Carbohydrate Research 2000; 329(3) 635-645.

[61] McCleary BV., Matheson NK., Small DM. Galactomannans and a galactoglucomannan in legume seed endosperms: Structural requirements for β-mannanase hydrolysis. Phytochemistry 1976;15(7) 1111-1117.

[62] Sims IM., Craik DJ., Bacic A. Structural characterisation of galactoglucomannan secreted by suspension-cultured cells of *Nicotiana plumbaginifolia*. Carbohydrate Research 1997; 303(1) 79-92.

[63] Anderson RF., Cadmus MC., Benedict RG., Slodki ME. Laboratory production of a phosphorylated mannan by *Hansenula holstii.* Archives of Biochemistry and Biophysics 1960; 89(2) 289-292.

[64] Poli A., Anzelmo G., Tommonaro G., Pavlova K., Casaburi A., Nicolaus B. Production and chemical characterization of an exopolysaccharide synthesized by psychrophilic yeast strain *Sporobolomyces salmonicolor* AL_1 isolated from Livingston island, Antarctica. Folia Microbiology 2010; 55(6) 576-581.

[65] Liu H., Wang Q., Liu Y., Fanf F. Statistical optimization of culture media and conditions production of mannan by *Saccharomyces cerevisiae*. Biotechnology and Bioprocess Engineering 2009; 14 577-583.

[66] Koilery SK., Keerthi TR. A study of morphological alterations of Meyerozyma guilliermondii cells during mannan synthesis. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2012; 3(2) 563-567.

[67] White LA., Newman MC., Cromwell GL., Lindemann MD. Brewers dried yeast as a source of mannan oligosaccharides for weanling pigs. Journal of Animal Science 2002; 80(10) 2619-2628.

[68] Chiura H., Iizuka M., Yamamoto T. A glucomannan as an extracellular product of Candida utilis. I. Production and characterization of a glucomannan. Agricultural and Biological Chemistry 1982; 46(7) 1723-1731.

[69] Frei E., Preston RD. Non-cellulosic structural polysaccharides in algal cell walls. II. Association of xylan and mannan in *Porphyra umbilicalis*. Peoceedings of the Royal Society Biological Sciences 1964;160(980) 314-327

[70] .Domozych DS., Ciancia M., Fangel JU., Mikkelsen MD., Ulvskov P., Willats WGT. The cell walls of green algae: a journey through evolution and diversity. Frontiers in Plant Science 2012; 3(82) 1-7.

[71] Kemmelmeier C., Zancan GT. Chemical and immunological properties of galactoglucomannana from *Dactylium dendroides*. Experimental Mycology 1981;5(3) 339-348.

[72] Cordeiro LMC. Polysaccharide productionby the chlorolichen *Pseeudocyphellaria clathrata*. The Bryologist 2005;108(1) 118-122.

[73] Carson KJ., Eagon RG. Cellular disintegration with concomitant release of slime and production of extracellular mannan by *Pseudomonas aeruginosa*: two separate phenomena. Canadian Journal of Microbiology 1964; 10(3) 467-472.

[74] Radchenkova N., Tomova A., Kambourova M. Biosynthesis of an exopolysaccharide produced by *Brevibacillus thermoruber* 438. Bionechnology & Biotechnology 2011; 25(4) 77-79.

[75] Liepman AH., Wilkerson CG., Keegstra K. Expression of cellulose synthase-like (*Csl*) genes in insect cells reveals that *CslA* family members encode mannan synthases. Proceedings of the National Academy of Sciences 2005;2 2221–2226.

[76] Bar-Peeled M., O'Neill MA. Plant nucleotide formation, interconversion, and salvage by sugar recycling. Annual Review of Plant Biotechnology 2011;62 127-155.

[77] Breton C., Mucha J., Jeanneau C. Structural and functional features of glycosyltransferases. Biochimie 2001;83 713-8.

[78] Breton C., Snajdrova L., Jeanneau C., Koca J., Imberty A. Structures and mechanisms of glycosyltransferases. Glycobiology 2006; 16(2) 29-37.

[79] Richmond T., Somerville CR. Integrative approaches to determining Csl function. Plant Molecular Bioogy. 2001;47 131–143.

[80] Hazen SP., Scott-Craig JS., Walton JD. *Cellulosesynthase-like* (*CSL*) genesofrice. Plant Physiology 2002;128 336–340.

[81] Dhugga KS., Barreiro R., Whitten B., Stecca K., Hazebroek J., Randhawa GS., Dolan M., Kinney AJ., Tomes D., Nichols S., Anderson P. Guarseed β-mannan synthase is a member of the cellulose synthase super gene family. Science 2004;303 363–366.

[82] Del Bem LE., Vincentz MG. Evolution of xyloglucan-related genes in green plants. BMC Evoutionary Bioogy 2010;10 341.

[83] Wang Y., Alonso AP., Wilkerson CG. Keegstra K. Deep EST profiling of developing fenugreek endosperm to investigate galactomannan biosynthesis and its regulation. *Plant Molecular Biology* 2012;79 243–258.

[84] Goubet F., Barton CJ., Mortimer JC., Yu X., Zhang Z., Miles GP., Richens J., Liepman AH., Seffen K., Dupree P. Cell wall glucomannan in *Arabidopsis* is synthesised by

CSLA glycosyltrans ferases, and influences the progression of embryogenesis. Plant Journal 2009;60 527–538.

[85] Verhertbruggen Y., Yin L., Oikawa A., Scheller HV. Mannan synthase activity in the CSLD family. Plant Signaling and Behaviour 2011;6 1620–1623.

[86] Doblin MS., DeMelis L., Newbigin E., Bacic A., Read SM. Pollen tubes of *Nicotiana alata* express two genes from different beta-glucan synthase families. Plant Physiology 2001;125 2040–2052.

[87] Favery B., Ryan E., Foreman J., Linstead P., Boudonck K., Steer M., Shaw P., Dolan L. *KOJAK* encodes a cellulose synthase-like protein required for root hair cell morphogenesis in *Arabidopsis*. Genes & Development 2001;15 79–89.

[88] Wang X., Cnops G., Vanderhaeghen R., DeBlock S., VanMontagu M., VanLijsebettens M. *AtCSLD3*, a cellulose synthase-like gene important for root hair growth in *Arabidopsis*. Plant Physiology 2001;126 575–586.

[89] Kim CM., Park SH., Je BI., Park SH., Park SJ., Piao HL., Eun MY., Dolan L., Han CD. *OsCSLD1*, a *Cellulose Synthase-Like D1* gene, is required for root hair morphogenesis in rice (*Oryzasativa* L.). Plant Physiology 2007;143 1220–1230.

[90] Bernal AJ., Yoo CM., Mutwil M., Jensen JK., Hou G.,Blaukopf C., Sorensen I.,Blancaflor EB., Scheller HV., Willats WG. Functional analysis of the *cellulose synthase-like* genes *CSLD1, CSLD2,* and *CSLD4* in tip-growing *Arabidopsis* cells. Plant Physiology 2008;148 1238–1253.

[91] Galway ME., Eng R.C., Schiefelbein JW., Wasteneys GO. Root hair-specific disruption of cellulose and xyloglucan in AtCSLD3 mutants, and factors affecting the post-rupture resumption of mutant root hair growth. Planta 2011;233 985–999.

[92] Park S., Szumlanski AL., Gu F., Guo F., Nielsen E. A role for CSLD3 during cell-wall synthesis in apical plasma membranes of tip-growing root-hair cells. Nature Cell Biology 2011;13 973–980.

[93] Wang Y., Mortimer JC., Davis J., Dupree P., Keegstra K. Identification of an adiitional protein involved in mannan biosynthesis. Plant Journal 2013; 73(1) 105-117.

[94] Edwards ME., Dickson CA., Chengappa S., Sidebottom C., Gidley MJ., Reid JSG. Molecular characterization of a membrane-bound galactosyltransferase of plant cell wall matrix polysaccharide biosynthesis. Plant Journal 1999; 19(6) 691-697.

[95] Gille S., de Souza A., Xiong G., Benz M., Cheeng K., Schultink A., Reca IB., Pauly M. O-acetylation of Arabidopsis hemicellulose xyloglucan requires AXY4 or AXY4L, proteins with a TBL and DUF231 domain. Plant Cell 2011; 23(11) 4041-4053.

[96] Gille S., Cheng K., Skinner ME., Liepman AH., Wilkerson CG., Pauly M. Deep sequencing of voodoo lily (*Amorphophallus konjac*): an approach to identify relevant

genes involved in the synthesis of the hemicellulose glucomannan. Planta 2011;234(3) 515-526.

[97] Dang JM., Leong KW. Natural polymers for gene delivery and tissue engineering. Advenced Drug Delivery Reviews 2006;58 487–499.

[98] Ratner BD., Bryant SJ. Biomaterials: Where we have been and where we are going. Annual Reviews of Biomedical Engineering 2004;6 41–75.

[99] Chen J., Jo S., Park K. Polysaccharide hydrogels for protein drug delivery. Carbohydrate Polymers 1995;28 69–76.

[100] Mizrahy S., Peer D. Polysaccharides as building blocks for nanotherapeutics. Chemical Society Reviews 2012;41, 2623–2640.

[101] Coviello T., Matricardi P., Marianecci C., Alhaique F. Polysaccharide hydrogels for modified release formulations. Journal of Controlled Release 2007;119 5–24.

[102] Cadée JA., Brouwer LA., den Otter W., Hennick WE., van Luyn MJ. A comparative biocompatibiltiy study of microspheres based on crosslinked dextran or poly(lacticcoglycolic) acid after subcutaneous injection in rats. Journal of Biomedical Materials Research 2001;56 600–609.

[103] Jain A., Gupta Y., Jain SK. Perspectives of biodegradable natural polysaccharides for site specific drug delivery to the colon. Journal of Pharmacy & Pharmaceutical Sciences 2007;10 86–128.

[104] Mehvar R. Recent trends in the use of polysaccharides for improved delivery of therapeutic agents: Pharmacokinetic and Pharmacodynamic perspectives. Current Pharmaceutical Biotechnology 2003;4 283–302.

[105] Alonso-Sande M., Teijeiro-Osorio D., Remuñán-López C., Alonso MJ. Glucomannan, a promising polysaccharide for biopharmaceutical purposes. European Journal of Pharmaceutics and Biopharmaceutics 2009;72 453–462.

[106] Kumar MN., Muzzarelli RA., Muzzarelli C., Sashiwa H., Domb AJ. Chitosan chemistry and pharmaceutical perspectives. Chemical Reviews 2004;104 6017–6084.

[107] Mourya VK.; Inamdar NN. Trimethyl chitosan and its application in drug delivery. Journal of Material Science: Materials in Medicine 2009;20 1057–1079.

[108] Thanou M., Verhoef JC., Junginger HE. Oral drug absorption enhancement by chitosan and its derivatives. Advenced Drug Delivery Reviews 200;52 117–126.

[109] Thanou M., Verhoef JC., Junginger HE. Chitosan and its derivatives as intestinal absorption enhancers. Advenced Drug Delivery Reviews 2001;50 S91–S101.

[110] Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. European Journal of Pharmaceutics and Biopharmaceutics. 2012;81(3):463-9.

[111] Boddohi S, Killingsworth CE, Kipper MJ. Polyelectrolyte multilayer assembly as a function of pH and ionic strength using the polysaccharides chitosan and heparin. Biomacromolecules. 2008;9(7):2021-8.

[112] Bonferoni M, Sandri G, Ferrari F, Rossi S, Larghi V, Zambito Y, et al. Comparison of different in vitro and ex vivo methods to evaluate mucoadhesion of glycol-palmitoyl chitosan micelles. Journal of drug delivery science and technology. 2010;20(6):419-24

[113] Reddy P, Chaitanya K, Madhusudan RY. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences. 2011;19(6).

[114] Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z. Polysaccharides-based nanoparticles as drug delivery systems. Advanced Drug Delivery Reviews. 2008;60(15):1650-62.

[115] Dai T, Tanaka M, Huang Y-Y, Hamblin MR. Chitosan preparations for wounds and burns: antimicrobial and wound-healing effects. 2011.

[116] Young E. The anti-inflammatory effects of heparin and related compounds. Thrombosis research. 2008;122(6):743-52.

[117] Sinha R, Kim GJ, Nie S, Shin DM. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. Molecular cancer therapeutics. 2006;5(8): 1909-17.

[118] Rubinstein A. Natural polysaccharides as targeting tools of drugs to the human colon. Drug development research. 2000;50(3-4):435-9.

[119] Vandamme TF, Lenourry A, Charrueau C, Chaumeil J. The use of polysaccharides to target drugs to the colon. Carbohydrate polymers. 2002;48(3):219-31.

[120] Lemarchand C, Gref R, Couvreur P. Polysaccharide-decorated nanoparticles. European Journal of Pharmaceutics and Biopharmaceutics. 2004;58(2):327-41.

[121] Sittikijyothin W., Torres D., Gonçalves MP. Modelling of the rheological behaviour of galactomannan aqueous solutionss. Carbohydrate Polymers 2005; 59 339.

[122] Srivastava M. Kapoor VP. Seed galactomannans: an overview. Chemical Biodiversity 2005;2 295–317.

[123] Gibson GR., Berry Ottaway P., Rastall RA., editor Prebiotics: New Developments in Functional Foods. Oxford: Chandos Publishing Limited; 2000.

[124] Hussein D., Helmy WA., Salem HM. Biological activities of some galactomannans and their sulfated derivatives. Phytochemistry 1998; 48 479-484.

[125] Sharon N., Ofek I. Safe as mother's milk: carbohydrates as future anti-adhesion drugs for bacterial diseases. Glycoconjugate Journal 2000;17 659–664.

[126] Titapoka S., Keawsompong S., Haltrich D., Nitisinprasert S. Selection and characterization of mannanase-producing bacteria useful for the formation of prebiotic manno-

oligosaccharides from copra meal. World journal of microbiology and biotechnology 2008;24(8) 1425-1433.

[127] Sato M, Ohshima T, Maeda N, Ohkubo C. Inhibitory effect of coated mannan against the adhesion of Candida biofilms to denture base resin. Dental materials journal. 2013;32(3):355-60.

[128] Shibata N, Okawa Y. Structure of Fungal Cell Wall Polysaccharides. Japanese Journal of Medical Mycology. 2006;47(3).

[129] Watanabe T, Takano M, Murakami M, Tanaka H, Matsuhisa A, Nakao N, et al. Characterization of a haemolytic factor from Candida albicans. Microbiology. 1999;145(3): 689-94.

[130] Calderone R. Molecular interactions at the interface of Candida albicans and host cells. Archives of medical research. 1992;24(3):275-9.

[131] Rotrosen D, Calderone RA, Edwards JE. Adherence of Candida species to host tissues and plastic surfaces. Review of Infectious Diseases. 1986;8(1):73-85.

[132] Iwamoto L, Watanabe T, Ogasawara A, Mikami T, Matsumoto T. [Adherence of Candida albicans is inhibited by yeast mannan]. Yakugaku zasshi: Journal of the Pharmaceutical Society of Japan. 2006;126(3):167-72.

[133] Butoescu N, Seemayer CA, Foti M, Jordan O, Doelker E. Dexamethasone-containing PLGA superparamagnetic microparticles as carriers for the local treatment of arthritis. Biomaterials. 2009;30(9):1772-80.

[134] Butoescu N, Jordan O, Burdet P, Stadelmann P, Petri-Fink A, Hofmann H, et al. Dexamethasone-containing biodegradable superparamagnetic microparticles for intra-articular administration: Physicochemical and magnetic properties, *in vitro* and *in vivo* drug release. European Journal of Pharmaceutics and Biopharmaceutics. 2009;72(3): 529-38.

[135] Munnier E, Cohen-Jonathan S, Linassier C, Douziech-Eyrolles L, Marchais H, Soucé M, et al. Novel method of doxorubicin–SPION reversible association for magnetic drug targeting. International journal of pharmaceutics. 2008;363(1):170-6.

[136] Lee KM, Kim S-G, Kim W-S, Kim SS. Properties of iron oxide particles prepared in the presence of dextran. Korean Journal of Chemical Engineering. 2002;19(3):480-5.

[137] Namgung R, Singha K, Yu MK, Jon S, Kim YS, Ahn Y, et al. Hybrid superparamagnetic iron oxide nanoparticle-branched polyethylenimine magnetoplexes for gene transfection of vascular endothelial cells. Biomaterials. 2010;31(14):4204-13.

[138] Yoo MK, Park IY, Kim IY, Park IK, Kwon J-S, Jeong H-J, et al. Superparamagnetic iron oxide nanoparticles coated with mannan for macrophage targeting. Journal of nanoscience and nanotechnology. 2008;8(10):5196-202.

[139] Stamopoulos D, Manios E, Gogola V, Benaki D, Bouziotis P, Niarchos D, et al. Bare and protein-conjugated Fe3O4 ferromagnetic nanoparticles for utilization in magnet-

ically assisted hemodialysis: biocompatibility with human blood cells. Nanotechnology. 2008;19(50):505101.

[140] Yallapu MM, Othman SF, Curtis ET, Gupta BK, Jaggi M, Chauhan SC. Multi-functional magnetic nanoparticles for magnetic resonance imaging and cancer therapy. Biomaterials. 2011;32(7):1890-905.

[141] Hayashi K, Ono K, Suzuki H, Sawada M, Moriya M, Sakamoto W, et al. High-frequency, magnetic-field-responsive drug release from magnetic nanoparticle/organic hybrid based on hyperthermic effect. ACS applied materials & interfaces. 2010;2(7): 1903-11.

[142] Sonoda A, Nitta N, Nitta-Seko A, Ohta S, Takamatsu S, Ikehata Y, et al. Complex comprised of dextran magnetite and conjugated cisplatin exhibiting selective hyperthermic and controlled-release potential. Int J Nanomedicine. 2010;5:499-504.

[143] Tsuchiya K, Nitta N, Sonoda A, Otani H, Takahashi M, Murata K, et al. Atherosclerotic imaging using 4 types of superparamagnetic iron oxides: New possibilities for mannan-coated particles. European journal of radiology. 2013;82(11):1919-25.

[144] Nakano M, Nakamura Y, Takikawa K, Kouketsu M, Arita T. Sustained release of sulphamethizole from agar beads. Journal of Pharmacy and Pharmacology. 1979;31(1): 869-72.

[145] Wang K, He Z. Alginate–konjac glucomannan–chitosan beads as controlled release matrix. International journal of pharmaceutics. 2002;244(1):117-26.

[146] Xiao C, Gao S, Wang H, Zhang L. Blend films from chitosan and konjac glucomannan solutions. Journal of Applied Polymer Science. 2000;76(4):509-15.

[147] Du J, Sun R, Zhang S, Govender T, Zhang LF, Xiong CD, et al. Novel polyelectrolyte carboxymethyl konjac glucomannan–chitosan nanoparticles for drug delivery. Macromolecular rapid communications. 2004;25(9):954-8.

[148] Du J, Zhang S, Sun R, Zhang LF, Xiong CD, Peng YX. Novel polyelectrolyte carboxymethyl konjac glucomannan–chitosan nanoparticles for drug delivery. II. Release of albumin in vitro. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2005;72(2):299-304.

[149] Alonso-Sande M, Cuña M, Remuñán-López C, Teijeiro-Osorio D, Alonso-Lebrero JL, Alonso MJ. Formation of new glucomannan-chitosan nanoparticles and study of their ability to associate and deliver proteins. Macromolecules. 2006;39(12):4152-8.

[150] Alonso-Sande M, Remuñán-López C, Alonso-Lebrero J, Alonso M, editors. Chitosan–glucomannan nanoparticles as carriers for oral administration of insulin: effect of glucomannan type and insulin loading. Proceedings of 32nd Meeting of the Controlled Release Society, Miami; 2005.

[151] Zhang X, Rogowski A, Zhao L, Hahn MG, Avci U, Knox JP, et al. Understanding How the Complex Molecular Architecture of Mannan-degrading Hydrolases Con-

tributes to Plant Cell Wall Degradation. Journal of Biological Chemistry. 2014;289(4): 2002-12.

[152] Avachat AM, Dash RR, Shrotriya SN. Recent investigations of plant based natural gums, mucilages and resins in novel drug delivery systems. Ind J Pharm Edu Res. 2011;45(1):86-99.

[153] Wu W-T, Cheng H-C, Chen H-L. Ameliorative effects of konjac glucomannan on human faecal β-glucuronidase activity, secondary bile acid levels and faecal water toxicity towards Caco-2 cells. British journal of nutrition. 2011;105(04):593-600.

[154] Connolly ML, Lovegrove JA, Tuohy KM. Konjac glucomannan hydrolysate beneficially modulates bacterial composition and activity within the faecal microbiota. Journal of Functional Foods. 2010;2(3):219-24.

[155] Kohyama K, Iida H, Nishinari K. A mixed system composed of different molecular weights konjac glucomannan and kappa carrageenan: large deformation and dynamic viscoelastic study. Food Hydrocolloids. 1993;7(3):213-26.

[156] Shen C, Li W, Zhang L, Wan C, Gao S. Synthesis of cyanoethyl konjac glucomannan and its liquid crystalline behavior in an ionic liquid. Journal of Polymer Research. 2012;19(1):1-8.

[157] Zhang C, Chen J-d, Yang F-q. Review: konjac glucomannan, a promising polysaccharide for OCDDS. Carbohydrate polymers. 2014.

[158] Li G, Qi L, Li A, Ding R, Zong M, editors. Study on the kinetics for enzymatic degradation of a natural polysaccharide, konjac glucomannan. Macromolecular Symposia; 2004: Wiley Online Library.

[159] Patel Parul K, Satwara Rohan S, Pandya S. Bacteria aided biopolymers as carriers for colon specific drug delivery system: A Review. International Journal of Pharm Tech Research. 2012;4:1192-214.

[160] Ancui M, Chengjun W, Yimin D, Jianwei G. Research on the Medicinal Polymer Material Konjac Glucomannan [J]. Journal of Dali University. 2009;2:004.

[161] Chen L-G, Liu Z-L, Zhuo R-X. Synthesis and properties of degradable hydrogels of konjac glucomannan grafted acrylic acid for colon-specific drug delivery. Polymer. 2005;46(16):6274-81.

[162] Xu D-Y, Li G-J, Liao Z-F, He X-H. Preparation and in vitro controlled release behavior of a novel pH-sensitive drug carrier for colon delivery. Polymer bulletin. 2009;62(2):183-93.

[163] Korkiatithaweechai S, Umsarika P, Praphairaksit N, Muangsin N. Controlled Release of Diclofenac from Matrix Polymer of Chitosan and Oxidized Konjac Glucomannan. Marine drugs. 2011;9(9):1649-63.

[164] Varshosaz J, Tavakoli N, Eram SA. Use of natural gums and cellulose derivatives in production of sustained release metoprolol tablets. Drug delivery. 2006;13(2):113-9.

[165] Dürig T, Fassihi R. Guar-based monolithic matrix systems: effect of ionizable and non-ionizable substances and excipients on gel dynamics and release kinetics. Journal of controlled release. 2002;80(1):45-56.

[166] Dey P, Maiti S, Biswanath S. Locust bean gum and its application in pharmacy and biotechnology: an overview. International Journal of Current Pharmaceutical Research. 2011;4:7-11.

[167] Vendruscolo C, Andreazza I, Ganter J, Ferrero C, Bresolin T. Xanthan and galactomannan (from< i> M. scabrella</i>) matrix tablets for oral controlled delivery of theophylline. International journal of pharmaceutics. 2005;296(1):1-11.

[168] Johnson I, Gee JM. Effect of gel-forming gums on the intestinal unstirred layer and sugar transport in vitro. Gut. 1981;22(5):398-403.

[169] Elsabbagh H, Sakr A, Abd-Elhadi S. Effect of guar gum on the dissolution rate of ephedrine hydrochloride and sulphadimidine tablets. Die Pharmazie. 1978;33(11): 730-1.

[170] Bhalla H, Shah A. Controlled release matrices for ketoprofen. Indian drugs. 1991;28(9):420-2.

[171] Bayliss C, Houston A. Degradation of guar gum by faecal bacteria. Appl Environ Microbiol. 1986;48:626-32.

[172] Macfarlane G, Hay S, Macfarlane S, Gibson G. Effect of different carbohydrates on growth, polysaccharidase and glycosidase production by Bacteroides ovatus, in batch and continuous culture. Journal of Applied Microbiology. 1990;68(2):179-87.

[173] Wong D, Larrabee S, Clifford K, Tremblay J, Friend D. USP dissolution apparatus III (reciprocating cylinder) for screening of guar-based colonic delivery formulations. Journal of controlled release. 1997;47(2):173-9.

[174] Lee SS, Lim CB, Pai CM, Lee S, Park I, Seo MG, et al. Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides. Google Patents; 2002.

[175] Pai C, Lim C, Lee S, Park I, Park H, Seomoon G, et al., editors. Pharmacoscintigraphic and pharmacokinetic evaluation of colon specific delivery system in healthy volunteers. Proceedings of the International Symposium on Controlled Release Bioactive Materials; 2000.

[176] Wakerly Z, Fell J, Attwood D, Parkins D. Pectin/ethylcellulose film coating formulations for colonic drug delivery. Pharmaceutical research. 1996;13(8):1210-2.

[177] Basit A. Oral colon-specific drug delivery using amylose-based film coatings. Pharmaceutical Technology Europe. 2000;12(2).

[178] Prasad Y, Krishnaiah Y, Satyanarayana S. In vitro evaluation of guar gum as a carrier for colon-specific drug delivery. Journal of controlled release. 1998;51(2):281-7.

[179] Krishnaiah Y, Satyanarayana S, Rama Prasad Y, Narasimha Rao S. Evaluation of guar gum as a compression coat for drug targeting to colon. International journal of pharmaceutics. 1998;171(2):137-46.

[180] Rubinstein A, Gliko-Kabir I. Synthesis and swelling-dependent enzymatic degradation of borax-modified guar gum for colonic delivery purposes. STP pharma sciences. 1995;5(1):41-6.

[181] Gliko-Kabir I, Yagen B, Penhasi A, Rubinstein A. Phosphated crosslinked guar for colon-specific drug delivery: I. Preparation and physicochemical characterization. Journal of controlled release. 2000;63(1):121-7.

[182] George M, Abraham T. pH sensitive alginate–guar gum hydrogel for the controlled delivery of protein drugs. International journal of pharmaceutics. 2007;335(1):123-9.

[183] Voepel J, Sjöberg J, Reif M, Albertsson AC, Hultin UK, Gasslander U. Drug diffusion in neutral and ionic hydrogels assembled from acetylated galactoglucomannan. Journal of Applied Polymer Science. 2009;112(4):2401-12.

[184] Roos AA, Edlund U, Sjoberg J, Albertsson A-C, Stålbrand H. Protein release from galactoglucomannan hydrogels: influence of substitutions and enzymatic hydrolysis by β-mannanase. Biomacromolecules. 2008;9(8):2104-10.

[185] Zou W, Liu C, Chen Z, Zhang N. Studies on bioadhesive PLGA nanoparticles: a promising gene delivery system for efficient gene therapy to lung cancer. International journal of pharmaceutics. 2009;370(1):187-95.

[186] Yu W, Liu C, Liu Y, Zhang N, Xu W. Mannan-modified solid lipid nanoparticles for targeted gene delivery to alveolar macrophages. Pharmaceutical research. 2010;27(8): 1584-96.

[187] Kong F, Ge L, Liu X, Huang N, Zhou F. Mannan-modified PLGA nanoparticles for targeted gene delivery. International Journal of Photoenergy. 2011;2012.

[188] Wu G, Zhou F, Ge L, Liu X, Kong F. Novel mannan-PEG-PE modified bioadhesive PLGA nanoparticles for targeted gene delivery. Journal of Nanomaterials. 2012;2012:11.

[189] Kaur A, Jain S, Tiwary AK. Mannan-coated gelatin nanoparticles for sustained and targeted delivery of didanosine: in vitro and in vivo evaluation. Acta pharmaceutica. 2008;58(1):61-74.

[190] Cui Z, Hsu C-H, Mumper RJ. Physical characterization and macrophage cell uptake of mannan-coated nanoparticles. Drug development and industrial pharmacy. 2003;29(6):689-700.

[191] Apostolopoulos V, McKenzie I, Wilson IA. Getting into the groove: unusual features of peptide binding to MHC class I molecules and implications in vaccine design. Frontiers in bioscience: a journal and virtual library. 2001;6:D1311-20.

IntechOpen